REMARKS

Claims 1-10, all of the pending claims in this application, are rejected in the Office Action dated April 1, 2008. Claims 1 and 2 have been amended to correct a typographical error: C=CH should be C≡CH as in the original PCT application. The typographical error was inadvertently introduced in the preliminary amendment dated July 21, 2004 when this application entered the National phase. Claim 2 has been amended to more clearly define the claimed process. Claim 11 has been added directed to the process of claim 1 wherein R2 is $(CH_2)_2OH$ as previously in claim 2. Support for new claim 11 can be found on page 4, line 16, of the specification and in claim 2 as originally filed. Applicants have amended the specification merely to include reference to the International Application of which the current application is a National stage application and the foreign application from which the International application claims benefit. Applicants submit that no new matter has been added by this amendment. Applicants respectfully request entry of the above amendments and reconsideration of the claims.

Priority

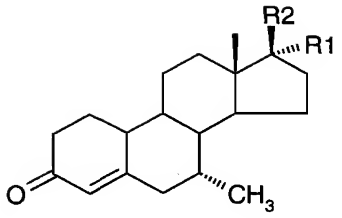
According to the Examiner, if applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. §371, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. In response applicants have amended the specification to include the requested references to prior applications. Further, applicants submit that the reference to the prior application was previously submitted but not in the first sentence of the specification, and the information concerning the benefit claim was recognized by the USPTO as shown by the inclusion thereof on the filing receipt. Accordingly, applicants submit that no petition or fees are required to enter the amendment to the specification to include the priority claims. Entry of the amendment to include the reference to the prior applications in the specification is respectfully requested.

Claims are Non-obvious

Claims 1-9 are rejected under 35 U.S.C. §103(a) as being allegedly obvious over Babcock et al (US 3,341,557), Campbell et al. (Steroids, 1963) and Loozen et al. (WO 01/05806). According to the Examiner each of Babcock et al and Campbell et al teaches the production of 7α-methyl derivatives of steroid compounds by reacting the corresponding 4,6-diene-ketone compounds with a methyl Grignard reagent in the presence of a cuprous salt. The Examiner further asserts that Campbell teaches selectivity and good yield of the 7α-methyl derivatives when the Grignard reagent is utilized in the presence of a cuprous salt. The Examiner asserts that the currently claimed invention differs by the reaction of a trialkylsilyl protected starting material in the process taught by each of Babcock et al and Campbell et al. However, according to the Examiner acyl groups and trialkylsilyl groups are known hydroxyl protecting groups. Moreover, the Examiner asserts that Loozen teaches 7α-alkylation of 4,6-diene-3-one steroid derivatives having trialkyl protecting groups as well as acyl protecting groups. Thus, the Examiner asserts the skilled artisan would have a reasonable expectation that the protection of the hydroxyl groups in the compounds taught by Babcock et al and Campbell et al with a trialkylsilyl group instead of an acetyl group would result in the production of the desired 7α-alkylation of the prior art compounds.

In response, applicants submit that subject matter in the Loozen et al reference, which constitute prior art only under 35 U.S.C. §102(e), and the currently claimed subject matter were commonly owned and under obligation to be assigned to the same person at the time the invention herein was made. Therefore, the cited Loozen et al reference does not constitute prior art for purposes of obviousness as under 35 U.S.C §103(c).

Further, applicants submit that the claimed process is for the preparation of 7α-methyl steroids of the formula I

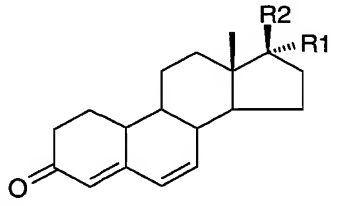


(I)

wherein R1 is hydrogen, methyl or C≡CH,

R2 is $(CH_2)_nOH$, wherein n is 0, 1 or 2;

by a copper mediated 1,6-conjugate addition of a Grignard reagent CH_3MgX, X being a halogen (Cl, Br or I), to the 4,6-unsaturated 3-ketosteroid of formula II,



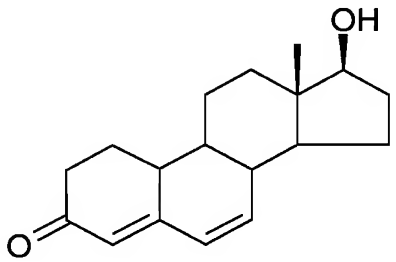
(II)

wherein R1 and R2 are as previously defined, comprising protecting the hydroxy group of the steroid of formula II with a trialkylsilyl group, whereby the alkyl group is defined as being a branched or unbranched alkyl group having 1 to 4 carbon atoms, followed by treating the hydroxy protected steroid with the Grignard reagent.

Babcock et al. (US 3,341,557) as well as Campbell et al., (Steroids, 1963), disclose cuprous halide catalyzed 1,6-conjugate addition of methyl magnesium bromide to 17-hydroxyl functional 4,6-unsaturated 3-ketosteroids, whereby the hydroxyl group is protected with an acetyl group. As described above, the presently claimed invention is directed to the stereoselective introduction of the methyl substituent at C-7. The methods published in Babcock et al. and Campbell et al. yield mixtures of the 7α- and 7β-methyl steroids in α,β-ratios ranging from 1.5:1 to 9:1 (page 2, lines 6 to 11 of the specification). Isolation of the pharmacological interesting 7α-isomers from the accompanying 7β-isomers can only be achieved by chromatographic separation or by laborious work-up procedures by repetitive recrystallization. Both operations decrease the yield of the desired 7α-isomer significantly.

In contrast to the methods in Babcock et al and Campbell et al the presently claimed invention provides a process wherein the α,β-ratio is significantly improved by protecting the 17-hydroxyl group of the steroid with a trialkyl silyl group during the reaction. As a result of this protection, surprisingly, a markedly improved stereo-selectivity of the Grignard reaction in favor of the desired 7α-methyl isomer is obtained. More particularly, levels of the unwanted 7β methyl-isomer are decreased to levels below 2.5% (α,β-ratio higher than 39:1). Thus, this claimed process provides for the first time a straightforward approach for increasing the stereoselectivity of 7α-isomers. Consequently, laborious work-up procedures by troublesome chromatographic separations or by repetitive recrystallization are unnecessary (page 4, lines 5 to 10, of the specification).

Further, in comparative experiments where the alkylation at the C-7 position is not a methylation but an ethylation using Δ^6 – nandrolone as the starting substrate (i.e. formula II in claim 1 wherein R1 is H and R2 is OH),



Δ^6 – nandrolone

copper mediated 1,6-conjugate additions of ethyl magnesium chloride of Δ^6 – nandrolone -17-trimethyl silyl ether were carried out. The reported selectivities were 83:17 with 2 equivalent of ethyl magnesium chloride and 63:37 with 7 equivalent ethyl magnesium chloride. Comparing the mixture of 7α- and 7β-alkylsteroids in α,β-ratios ranging from 1.5:1 to 9:1 obtained in copper mediated 1,6-conjugate additions of methyl magnesium bromide of 17-hydroxyl functional 4,6-unsaturated 3-ketosteroids, whereby the hydroxyl group is protected with an acetyl group according to Babcock et al or Campbell et al with the above-mentioned results of 63:37 and 83:17 in copper mediated 1,6-conjugate

additions of ethyl magnesium chloride of 17-hydroxyl functional 4,6-unsaturated 3-ketosteroids whereby the hydroxyl group is protected with a silyl group, the skilled artisan would not consider the replacement of the acetyl group by the silyl group in the expectation to obtain improved results, i.e. a decrease of the unwanted 7β methyl-isomer to levels below 2.5% (α,β-ratio higher than 39:1).

Moreover, the current specification (page 5, line 29 to page 6, line 5) describes a comparison of preparing MENT, wherein one intermediate is prepared according to the claimed process with a process wherein the same intermediate is prepared without the introduction of the trialkylsilyl protective group (herein is made reference to the process as in US 5,342,834 which in turn refers to a process as in Babcock et al with an acetyl protecting group (US 5,342,834, col. 2, lines 57-61)). In the process without the introduction of the trialkylsilyl protective group an initial yield for MENT of approximately 55%, with a 7α,β-ratio of 85:15 was obtained and after isolation of the 7α-isomer the overall yield decreased to 44%. In contrast, the process according to the invention, using the introduction of the trialkylsilyl protective group as in example 1, resulted in MENT with a 7α,β-ratio of 99:1 and an overall yield increasing to 79%. This is an improvement of the overall yield by 80%.

In view of the above, Applicant is of the opinion that a person skilled in the art would not have expected that the replacement of the acetyl group in Babcock et al or Campbell et al by a silyl group would lead to the improved results of stereoselectivity mentioned by Applicant, i.e. an α,β-ratio higher than 39:1 with respect to the desired 7α-methyl isomer. For all of these reasons, Applicants respectfully request withdrawal of the rejection of claims 1-9 over Babcock et al, or Campbell et al and Loozen et al under 35 U.S.C. §103(a).

Claim 10 is rejected under 35 U.S.C. §103(a) as being allegedly obvious over Peters et al (WO 01/58919). The Examiner asserts that Peters et al teaches the syntheses of steroids having anti-estrogenic and other therapeutic properties. Further, the Examiner asserts that Peters et al teaches several compounds useful as intermediates in the

disclosed syntheses including compounds of formulae XXI and XXVIII. According to the Examiner the claimed invention differs by reciting a compound not exemplified in the reference, however the reference teaches the acetyl derivative of the claimed compound and teaches hydroxymethyl or a protected hydroxymethyl group in the 21-position. The Examiner asserts that therefore the claimed compound would have been obvious to the skilled artisan because there would be a reasonable expectation that replacing compound 9 with the free alcohol derivative would result in the production of the corresponding free alcohol derivative of compound 10.

In response, applicants submit that Peters et al teaches 7α-alkylation using a lower alkyl lithium in the presence of lithium bromide wherein the hydroxyl moiety is protected with a suitable protecting group. This process differs from the process of the current application. Further, a suitable protecting group as in Peters et al includes an alkyl, acetyl, mesylate (Ms), tosylate (Ts), and THP. More specifically, Peters et al teaches that particularly the "use of acetate as the Pr^1 protecting group greatly facilitates the addition of the 7-alkyl group in the α-position." Peters et al reasons that "[w]hile not wishing to be limited by theory, it is believed that the acetate moiety forms a complex with the lithium and promotes introduction of the 7-alkyl functionality from the α-face of the steroid" (Peters et al page 20, lines 23-26). Accordingly, Peters et al teaches the use of an acetate protecting group in a process using alkyl lithium in the presence of lithium bromide to a 7α-alkylated steroid. Considering the difference in 7α-alkylation processes and Peters et al's preference for an acetate protecting group, there is no motivation in Peters et al to modify the compound of formula XXI to obtain the claimed compound of a free alcohol intermediate which may be used to prepare the trialkylsilyl protected substrate for process of the current application.

In view of the above, applicants submit that in contrast to the Examiner's assertions Peters et al provides no motivation to the skilled artisan to modify the compound of formula XXI to arrive at the claimed compound. Therefore, Applicants respectfully request withdrawal of the rejection of claim 10 over Peters et al under 35 U.S.C. §103(a).

In view of the above amendment and remarks, Applicants believes the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

Dated: October 1, 2008

Respectfully submitted,

By 

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